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Translation

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/FR2003/000157	International filing date (*day/month/year*) 17 janvier 2003 (17.01.2003)	Priority date (*day/month/year*) 18 janvier 2002 (18.01.2002)
International Patent Classification (IPC) or national classification and IPC C12N 5/06		
Applicant GENFIT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04 août 2003 (04.08.2003)	04 February 2004 (04.02.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/000157

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-41, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-42, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/4-4/4, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-42	YES
	Claims		NO
Inventive step (IS)	Claims	1-14, 17, 18, 23-26, 36, 37, 42	YES
	Claims	15, 16, 19-22, 27-35, 38, 39-41	NO
Industrial applicability (IA)	Claims	1-42	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: Chawla et al, 1993, JBC, 268(22): 16265-16269;
D2: Gervois et al, 1999, Mol. Endo, 13(3): 400-409;
D3: Austin et al, 1998, Cell Growth & Dif., 9: 267-276;
D4: Fontaine et al, 2003, JBC, 278(39): 37672-37680.

D4 was not cited in the international search report.

Inventive step

Adipocyte differentiation is a complex process that is controlled in a coordinated manner by a network of multiple transcription factors that induce the expression of PPAR GAMMA, which is the main coordinator of adipocyte differentiation (see the description, page 2, lines 13-22).

It has been demonstrated that the REV-ERB ALPHA receptor is induced during adipocyte differentiation and that such induction is caused by a transcription mechanism (see **D1**, the abstract, page 16266, left-hand column, fifth paragraph to page 16268, right-hand column, first

paragraph; figures 1-3).

In addition, in HepG2 liver cells, REV-ERB ALPHA transcription (see **D2**, page 401, right-hand column, first paragraph to page 403, left-hand column, last paragraph; figure 1) is increased by PPAR ALPHA, which binds to the REV-DR2 site of REV-ERB ALPHA. In said document, HepG2 cells were transfected with a construct comprising a reporter gene and a fragment of the REV-ERB ALPHA promoter in the presence of a vector enabling PPAR ALPHA expression, and the induction of REV-ERB ALPHA gene transcription by fibrates was tested (see figure 2).

Finally, the transfection of 3T3-L1 pre-adipocyte cells with a REV-ERB ALPHA expression vector is described in **D3** (see page 271, left-hand column, last paragraph to page 272, left-hand column, third paragraph; figures 7 and 8; page 275, left-hand column, second paragraph).

In view of the above, it is a routine technical step for a person skilled in the art to combine all of the features disclosed in claims 15, 16, 19-22, 27-35, 38 and 39-41 with the teachings of documents **D1-D3**:

The method of claims 15 and 16 differs from the one described in **D2** (see figure 2 and page 402, left-hand column to page 403, left-hand column) in that a vector comprising PPAR GAMMA and HepG2 cells is used. Since some of the genes targeted by PPAR ALPHA and PPAR GAMMA are the same, a person skilled in the art would have been prompted to discover whether the PPAR GAMMA receptor also binds to the REV-ERB2 site of REV-ERB ALPHA and would thereby have arrived at the same results as the invention.

The 3T3-L1 pre-adipocyte cells described in **D3** differ from

those in claims 19-22, 27-35, 38 and 39-41 by virtue of the nucleic acid sequences added to the vector. Since there are no special technical features constituting a technical improvement over the prior art, the proposed cells are an alternative solution to a known method for producing 3T3-L1 pre-adipocyte cells transfected with REB-ERV ALPHA and provide the same or similar effects.

It follows that the subject matter of claims **15, 16, 19-22, 27-35, 38** and **39-41** does not involve an inventive step (PCT Article 33(3)).

Further observations

1. The present claims 1-14, 15 and 16 relate to a method for identifying compounds defined by reference to a desirable feature or property thereof, namely the ability of said compounds to modulate adipocyte differentiation. The claims cover all methods that have this feature or property, yet the application only provides support under the terms of PCT Article 6 and/or a disclosure under the terms of PCT Article 5 for a very limited number of such methods. In the present case, the lack of support for the claims and of disclosure for the application is such that it is impossible to carry out a meaningful examination of the entire scope covered by the claims. Irrespective of the reasons set out above, the claims also lack clarity. Indeed, the claims attempt to define the method in terms of the result to be achieved. In the present case, this lack of clarity is again such that it is impossible to carry out a meaningful examination of the entire scope covered by the claims. As a

result, the examination has only been carried out with respect to those parts of the claims with subject matter that appears to be clear, supported and sufficiently disclosed, namely those parts relating to the methods mentioned in the examples on pages 33-40, i.e. those relating to the generation of stable pre-adipocytes, particularly 3T3-L1 cells, infected with a retroviral vector carrying all of the cDNA coding for the REV-ERB ALPHA receptor; and the expression of REV-ERB ALPHA on said cell lines in the presence of rosiglitazone (PPAR GAMMA ligand), as measured by immunocytochemical analyses or Western blot.

2. Claims 17 and 18 relate to compounds capable of modulating adipocyte differentiation. These claims do not fulfil the requirements of PCT Article 6 in so far as the subject matter for which protection is sought has not been clearly defined in structural terms (i.e. agonists or antagonists of the REV-ERB ALPHA receptor). Contrary to the requirements of PCT Article 6, said claims are not supported by the description since their scope is broader than that justified by the description and the drawings.

The claims are speculative and attempt to define the subject matter thereof in terms of the result to be achieved, yet this merely amounts to stating the basic problem that the invention is intended to solve.

It should be noted that, in **D4** (publication in the present application), the inventors suggest that REV-ERB ALPHA may have a role in adipogenesis, but the molecular mechanisms by means of which REV-ERB

ALPHA increases adipogenesis remain unknown (see the discussion, page 37679, right-hand column, last paragraph to page 37680, left-hand column, second paragraph).